REMARKS

Claims 38, 41-43, 45, 46, 48-59, 62, 65, 66, 69, 70, 71, 73, 74, 76-86, 89, 90, 93, 116-124 and 131 are pending. Claims 39-40, 44, 47, 60, 63, 64, 67-68, 72, 75, 87, 88, 91, 92, 94-115 and 125 have been canceled. Claims 38, 41, 43, 45, 46, 48-54, 62, 65, 66, 69, 71, 73, 74, 76-82, 89, 90, 93, 117 and 124 have been amended. Support for the claim amendments an be found throughout the application as originally filed. No new matter has been added.

Objection to the Specification

The specification is objected to because the trademarks used in the specification "should be capitalized … and be accompanied by generic terminology."

The specification has been amended to properly identify the trademarks recited in the application, thereby obviating this objection.

Rejection Under 35 U.S.C. §102(b)

Claims 38-41, 48, 49, 64, 65 and 116 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Liu *et al.* (Biochemistry, 1979, 18, 690-697). At page 3, section 6 of the Office Action, the Office states

> Liu *et al.* teach *m*-maleidobenzoylinsulin (MB-insulin) …. MB-insulin was synthesized through the reaction of porcine insulin with *m*-maleidobenzyol-N-hydroxysucciminimide ester (MS). The hydroxysuccinimide group reacts with free amino groups on insulin to yield insulin linked to a maleimido-containing group by a benzoyl linker. Free amino acids on insulin include the N-terminal amino groups of the A and B chain and the side chain of lysine B29. … Because the structure of the insulin derivative taught by Lui *et al.* is identical to the claimed derivative, the prior art of Lui *et al.* inherently meets this functional limitation.

Claims 39-40 have been cancelled. Claims 38, 41, 48, 49, 65 and 116, as amended, recite an insulin derivative that includes an insulin molecule and a reactive group for covalently bonding an albumin, the reactive group being a maleimido-containing group that is coupled to an α-amino group of the N-terminus amino acid of the B chain of the insulin molecule. Thus, the claims recite that the maleimido-containing reactive group reacts with only one of the several available amine groups. The maleimido-containing reactive group is coupled only to the α-amino group of the N-terminus of the B chain of the insulin molecule.

Liu et al. do not inherently anticipate the insulin derivative recited in the amended claims. Liu et al. react *m*-maleidobenzyol-N-hydroxysucciminimide with insulin. None of the amino groups of the insulin molecule used by Liu et al. appear to be protected prior to the reaction of the *m*-maleidobenzyol-N-hydroxysucciminimide with the insulin molecule. Therefore, the methods disclosed by Liu et al. can result a maleimido-containing group being coupled to any one of the available amino groups present in insulin.

As provided in section 2112 of the Manual for Patent Examination Procedures (MPEP), "To establish inherency, the extrinsic evidence 'must make it clear that the missing descriptive matter is necessarily present in the thing described in the reference' .... Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient."

As discussed above, the methods disclosed by Liu et al. do not necessarily result in a maleimido-containing reactive group being coupled to the α amino group at the N-terminus of the B chain of an insulin molecule. Therefore, Liu et al. do not inherently anticipate the claims as amended.

Applicants respectfully request that the Office withdraw this rejection.

Rejection Under 35 U.S.C. §103(a)

The Office rejects claims 38-125 and 131 under 35 U.S.C. §103(a) as allegedly being unpatentable over Bridon et al. (WO 00/69900) in view of Jones et al. (WO 95/05187), Jonassen et al., Baudys et al. Bridon et al. and Vajo et al. According to the Office,

> It would have been obvious to one of ordinary skill in the art to apply the method for the coupling of therapeutic peptides to the reactive moiety maleimidopropionic acid taught by Bridon et al. (WO 00/69900 and CA 2363712) to insulin and to use the resulting MPA-derivatized insulin to react with the blood protein albumin to form a stable insulin albumin covalent complex according to the method of albumin conjugation taught by Bridon et al. (WO 00/69900 and CA 2363712). The skilled artisan would have coupled the MPA to one of three free amino groups in insulin: the N-terminal alpha-amino group of the A and B chains, or the epsilon-amino group of the lysine B29 side chain based upon the MPA reaction taught by Bridon et al. (WO 00/69900) and Bridon et al. (CA 2363712).

The claims currently pending in the present application are directed to an insulin derivative that includes an insulin molecule and a maleimido-containing reactive group. The reactive group is selectively coupled to the N-terminus amino acid of the B chain of the insulin molecule. The claims, as amended, are patentable over the references cited by the Office.

I. It was not predictable that albumin covalently bound to insulin via a maleimido-containing reactive group at the N-terminal amino acid of the B chain of insulin would bind and activate the insulin receptor much less that it would exhibit significantly better binding affinity when compared to albumin covalently bound to insulin at other available positions

Applicants have found that conjugation of albumin via a maleimido-containing reactive group to the N-terminal amino acid of the B chain of insulin results in a significant increase in binding affinity to the insulin receptor as compared to conjugates having albumin attached via a maleimido-containing reactive group to either the N-terminal amino acid of the A chain or the lysine at position 29 of the B chain of the insulin molecule.

The present application provides various examples of albumin conjugated via a maleimido-containing reactive group to various positions within the insulin molecule. These include 1) MPA covalently bound to the α amino group at the N-terminus amino acid of the A chain of insulin (also referred to as "(Gly A1)-MPA-Insulin"); 2) MPA covalently bound to the α amino group at the N-terminus amino acid of the B chain of insulin "(Phe B1)-MPA-Insulin"); 3) MPA covalently bound via an octanoic acid linker (OA) to the α amino group at the N-terminus amino acid of the B chain of insulin "(Phe B1)-MPA-OA-Insulin"); 4) MPA covalently bound to the ε amino group of the lysine at position 29 of the B chain of insulin "(Lys B29)-MPA-Insulin"); 5) MPA covalently bound via an AEES linker to the α amino group at the N-terminus amino acid of the B chain of insulin "(Phe B1)-MPA-$(AEES)_2$-Insulin"); 6) MPA covalently bound via an AEES linker to the ε amino group of the lysine at position 29 of the B chain of insulin "(Lys B29)-MPA-$(AEES)_2$-Insulin"); and 7) MPA covalently bound via an OA linker to the ε amino group of the lysine at position 29 of the B chain of insulin "(Lys B29)-MPA-(OA)-Insulin"). As shown in Example IX of the application and the Table provided below, conjugation of albumin via a maleimido-containing reactive group to the N-terminal

amino acid of the B chain of insulin results in an albumin-insulin conjugates that have a significantly better binding affinity to the insulin receptor.

Table I.

Conjugate	IC50 (nM)
(Gly A1)-MPA-Insulin	2059.0
(Phe B1)-MPA-Insulin	100.5
(Phe B1)-MPA-OA-Insulin	87.7
(Lys B29)-MPA-Insulin	1190.0
(Phe B1)-MPA-$(AEES)_2$-Insulin");	38.5
(Lys B29)-MPA-$(AEES)_2$-Insulin	508.2
(Lys B29)-MPA-(OA)-Insulin	1013.4

Thus, the claimed insulin derivatives conjugated to albumin via a maleimido-containing reactive group at the N-terminal amino acid of the B chain of insulin results in a 5 to over 50 fold increase in binding affinity to the insulin receptor as compared to insulin derivatives having albumin attached via a maleimido-containing reactive group to either the N-terminal amino acid of the A chain or the lysine at position 29 of the B chain of the insulin molecule. This result could not have been predicted by either of the Bridon et al. references much less by any of the other references cited by the Office.

i. Bridon et al. (WO 00/69900) do not recite the synthesis of an insulin derivative or albumin conjugate thereof much less that albumin conjugated to insulin via a maleimido-containing reactive group at the N-terminal amino acid of the B chain of insulin would have a significantly higher binding affinity for the insulin receptor as compared to albumin conjugated to insulin at other available positions

As acknowledged by the Office at page 5, section 10 of the Office Action "Bridon *et al.* does not explicitly recite the synthesis of the insulin derivative or conjugate." Bridon et al. (WO 00/69900) also does not teach or suggest conjugation of albumin via a maleimido-containing reactive group to the N-terminal amino acid of the B chain of insulin over other available amino groups of insulin. Furthermore, nothing in the Bridon et al. (WO 00/69900) reference would have suggested that albumin conjugated via a maleimido-containing reactive group to the N-terminal amino acid of the B chain of insulin would bind and activate the insulin receptor with a

5 to over 50 fold better binding affinity than albumin conjugated via a maleimido-containing reactive group to other available position in the insulin molecule. This result was not predictable.

ii. Bridon et al. (CA 2363712) do not teach or suggest an insulin derivative or an insulin derivative-albumin conjugate thereof much less that albumin conjugated to insulin via a maleimido-containing reactive group at the N-terminal amino acid of the B chain of insulin would have significantly better binding affinity for the insulin receptor when compared to albumin conjugated to insulin at other available positions

Bridon et al. (CA 2363712) disclose that a maleimido-containing reactive group can form a covalent bond with serum albumin to stabilize ***an insulinotrophic hormone*** which are peptides that have a very different structure and mechanism of action than insulin. Insulin is very different from the insulinotrophic peptides of Bridon et al. (CA 2363712).

The insulinotrophic peptides GLP-1, exendin 3 and exendin 4 bind the GLP-1 receptor. The binding of these peptides to the GLP-1 receptor results in an intracellular signal. The intracellular signal is not the insulinotrophic peptide itself but a different molecule produced in response to the binding of the insulinotrophic peptide to the GLP-1 receptor. The intracellular signal results in the production of insulin. The insulin produced due to the intracellular signal has an anti-diabetic effect.

Insulin functions very differently. To have its anti-diabetic effect, insulin must not only bind its receptor but the insulin itself must be internalized. Thus, the insulin itself creates an anti-diabetic effect.

In addition, the insulinotrophic peptides disclosed by Bridon et al. (CA 2363712) are small linear peptides. In contrast, insulin is a highly organized three dimensional structure with three disulfide bonds. Based upon the differences in structure and function of insulinotrophic peptides and insulin, it would not be obvious to one of ordinary skill to use the approach disclosed in Bridon et al. (CA 2363712) to produce the claimed insulin molecule. One of ordinary skill in the art would not expect, based upon the teachings of Bridon et al. (CA 2363712), that insulin, a complex three dimensional protein, covalently bound with a protein, especially a protein as large as albumin, would bind its receptor with sufficient affinity and be internalized into a cell such that the insulin would have an anti-diabetic effect.

Furthermore, nothing in the Bridon et al. (CA 2363712) reference teaches or suggests conjugation of albumin via a maleimido-containing reactive group to the N-terminal amino acid of the B chain of insulin over other available positions in insulin. Nothing in the Bridon et al. (CA 2363712) reference taught or suggested that albumin conjugated via a maleimido-containing reactive group to the N-terminal amino acid of the B chain of insulin would bind and activate the insulin receptor with 5 to over 50 fold better binding affinity than albumin conjugated via a maleimido containing reactive group to other available position in the insulin molecule.

II. The remaining references cited by the Office do not provide any teaching or suggestion to covalently bind albumin via a maleimido-containing reactive group to the N-terminal amino acid of the B chain of insulin much less that albumin covalently bound to insulin at this position would have significantly better binding affinity for the insulin receptor when compared to albumin conjugated to insulin at other available positions

The Office cites Jones et al., Jonassen et al. and Baudys et al. for their teaching of "insulin conjugation chemistry". However, nothing in any of these three references teaches or suggests covalently binding albumin via a maleimido-containing reactive group that is coupled to the N-terminal amino acid of the B chain of insulin. In fact, Jones et al., Jonassen et al. and Baudys et al. all disclose insulin linked to another moiety by a non-covalent bond and/or linked to another moiety at a position other than the N-terminus amino acid of the B chain of insulin.

For example, Jonassen et al. disclose the use of fatty acids to ***non-covalently*** bind the ***lysine at position 29*** of the B chain of insulin to serum albumin. Jones et al. disclose use of thyroxine to ***non-covalently*** bind a blood protein to the N-terminal amino acid of the B chain of insulin. Baudys et al. disclose the covalent bonding of carboxymethyl dextan to the N-terminal amino acid of the ***A chain of insulin***.

Many of the secondary references cited by the Office suggest attaching a moiety to insulin at either the N-terminal amino acid of the A chain of insulin or at the lysine at position 29 of the B chain of insulin. As discussed in detail above, Applicants have shown that albumin covalently bound to the N-terminal amino acid of the B chain of insulin results in an albumin conjugate that has a significantly better binding affinity for the insulin receptor than albumin covalently bound to insulin at other available positions.

The remaining secondary references cited by the Office disclose non-covalent association of insulin with a blood protein. That bond disassociates so that insulin only, and not the blood protein such as albumin, is internalized. The internalized insulin (that is ***not*** attached to the blood protein) has the anti-diabetic effect.

In contrast, the claimed insulin conjugates are covalently bound to albumin. Thus, the insulin and albumin of the claimed insulin conjugates must be internalized with albumin attached for insulin to have its anti-diabetic effect. These two approaches are not interchangeable.

The remaining reference cited by the Office, Vajos et al., merely discloses the use of native insulin and the insulin analogs lispro, aspart, and glargine as examples of insulins for the treatment of diabetes. This reference does not make up for the deficiencies of the other references cited by the Office.

III. Summary

It was not predictable that conjugation of albumin to insulin via a maleimido-containing reactive group at the N-terminus amino acid of the B-chain would result in an insulin-albumin conjugate that binds to and activates the insulin receptor with an affinity 5 to over fifty fold greater than albumin conjugated via a maleimido-containing group to other available positions of insulin. Furthermore, it was not predictable that insulin, a complex three dimensional protein, covalently bound with a protein as large as albumin, would bind its receptor with sufficient affinity and be internalized into a cell such that the insulin would have an anti-diabetic effect.

For at least the reasons provided above, the claims are patentable over the references cited by the Office. Applicants respectfully request that the Office withdraw this rejection.

Obviousness Type Double Patenting Rejection

Claims 38-41, 43-69, 71-117 and 131 are rejected on the ground of nonstatutory obviousness type double patenting as allegedly being unpatentable over claim 44 of copending U.S. Patent Application No. 11/112,277. According to the Office, "claim 26 of copending application 11/112,277recites insulin derivatives comprising an insulin molecule and a reactive

maleimido-containing group for covalent bonding to a blood protein .... The insulin derivatives and albumin conjugates rejected in claim 26 anticipate the instant claims."

Applicants respectfully traverse this rejection. However this rejection does not need to be addressed since U.S. Patent Application No. 11/112,277 has now issued as U.S. Patent Number 7,307,277. Claim 26 of the issued patent does not recite an insulin derivative or conjugate. Therefore, this rejection is moot.

Claims 38-41, 43-69, 71-117 and 131 are provisionally rejected on the ground of nonstatutory obviousness type double patenting as allegedly being unpatentable over claim 44 of copending U.S. Patent Application No. 11/981,474. Upon indication of allowable subject matter in this application or the pending application cited by the Office, Applicants will address this rejection.

Claims 42 and 70 are provisionally rejected on the ground of nonstatutory obviousness type double patenting as allegedly being unpatentable over claim 44 of copending U.S. Patent Application No. 11/981,474, in view of Vajo *et al.*, (*Endocrine Rev.*, 2001, 22, 706-717). Upon indication of allowable subject matter in this application or the pending application cited by the Office, Applicants will address this rejection.

Claims 118-125 are provisionally rejected on the ground of nonstatutory obviousness type double patenting as allegedly being unpatentable over claim 44 of copending U.S. Patent Application No. 11/981,474, in view of Bridon *et al.*, (CA 2363712). Upon indication of allowable subject matter in this application or the pending application cited by the Office, Applicants will address this rejection.

Claims 38-125 and 131 are provisionally rejected on the ground of nonstatutory obviousness type double patenting as allegedly being unpatentable over claims 26-49 of copending U.S. Patent Application No. 11/982,033, in view of Bridon *et al.*, (WO 00/69900), Jones *et al.*, (WO 95/05187), Jonassen *et al.*, (Peptide Science: Present and Future, Proceedings of the International Peptide Symposium, Kyoto, 1997, pages 647-677), Baudys *et al.*, (*Bioconjugate Chemistry*, 1998, 9:176-183), Bridon *et al.*, (CA 2363712) and Vajo *et al.*, (*Endocrine Rev.*, 2001, 22, 706-717). Upon indication of allowable subject matter in this application or the pending application cited by the Office, Applicants will address this rejection.

Claims 38-125 and 131 are provisionally rejected on the ground of nonstatutory obviousness type double patenting as allegedly being unpatentable over claims 1-58 of copending U.S. Patent Application No. 11/645,297, in view of Bridon *et al.*, (WO 00/69900), Jones *et al.*, (WO 95/05187), Jonassen *et al.*, (Peptide Science: Present and Future, Proceedings of the International Peptide Symposium, Kyoto, 1997, pages 647-677), Baudys *et al.*, (*Bioconjugate Chemistry*, 1998, 9:176-183), Bridon *et al.*, (CA 2363712) and Vajo *et al.*, (*Endocrine Rev.*, 2001, 22, 706-717). Upon indication of allowable subject matter in this application or the pending application cited by the Office, Applicants will address this rejection.

CONCLUSION

For at least the reasons set forth above, Applicants submit that all grounds for rejection have been overcome and that all claims are now in condition for allowance, which action is respectfully requested.

A Petition for Extension of Time and the required fee are being submitted concurrently herewith on the Electronic Filing System (EFS). Please apply any other charges or credits to deposit account no. 50/2762, referencing Attorney Docket No. C2077-7016US.

Respectfully submitted,
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